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Session 4: Resistant Hypertension

Treatment-resistant hypertension: The challenges for drug treatment

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Resistant hypertension is present in patients who have a blood pressure above target despite treatment with 3 or more drugs, including a diuretic. Poor adherence to treatment is a major factor to explore before making a reliable diagnosis of treatment-resistant hypertension (TRH). Directly observed therapy and ambulatory blood pressure monitoring are important adjuncts to this diagnosis, which is clinically important because people with TRH have poor cardiovascular outcomes. After combining an ACE inhibitor/ARB, calcium antagonist and diuretic, cheap and effective next steps include additional diuretic therapy, a mineralocorticoid antagonist, an alpha-adrenoceptor antagonist or beta-adrenoceptor antagonist. Currently, it is not clear which approach offers the greatest benefit. More recently, endothelin (ET) receptor antagonists (ETRAs) have undergone clinical trials in this indication; in particular the landmark studies with darusentan (DORADO and DORADO-AC). Although most observers would argue that darusentan was both safe and effective in this indication [1], the drug failed to achieve its predetermined primary endpoint in phase 3 trials, and the drug was not take forward. Together with data from studies with bosentan in primary hypertension, sitaxentan in hypertensive chronic kidney disease, and atrasenten in diabetic nephropathy, these agents seem not only to lower blood pressure, but also to reverse arterial stiffness, endothelial dysfunction and renal dysfunction (in terms of a proteinuria surrogate). On the other hand, ETRAs cause fluid retention and are teratogenic, and the balance of efficacy against safety and cost (now low for what are mostly generic drugs) remains unclear. While there may still be a market for a new agent in TRH, drug therapy will now have to compete with devices such as those used in renal denervation therapy and baroreceptor stimulation therapy.

[1] Webb DJ. DORADO: opportunity postponed: lessons from studies of endothelin receptor antagonists in treatment-resistant hypertension. Hypertension 2010];56:806–7.

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Impact of neuromodulation on pressure dysregulation — From hypertension to hypotension

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In the human body, all cells, tissues, organs, and systems operate coherently. The presence of well- developed neurohumoral communications among these components of the body is the essential infrastructure that makes coherent functioning possible. Since the design goal of the cardiovascular system is to provide adequate perfusion to peripheries, the normal operation of cardiovascular regulator y system is vital. Recent investigations indicated that the neurohumoral regulator y system plays a central role in the pathogenesis of refractory cardiovascular disease such as hypertension, hypotension and heart failure. The fact that one cannot sustain arterial pressure even for a few seconds in the upright position without baroreflex indicates that pressure stabilization is an essential requirement to maintain homeostasis. Hence the vasomotor center in the brainstem regulates the cardiovascular system mainly through the autonomic nervous system, we may be able to intervene the function of cardiovascular system nonpharmacologically if we can artificially modulate the autonomic nerves. The case of central baroreflex failure is an archetypal pathophysiology requiring such an intervention. In treating this disease, it is conceivable that one can implement an artificial baroreflex system as a kind of biological proxy capable of emulating the native central baroreflex function of the failing vasomotor center. The artificial baroreflex system consists of a pressure sensor, microprocessor and nerve stimulator for activation of sympathetic efferent nerves. The system operates as an intelligent negative feedback regulator, and has been demonstrated early in the 2000s to be effective in restoring normal baroreflex functioning. The clinical impact of direct manipulation of autonomic functions is very profound, particularly in the treatment of refractory cardiovascular disease. We would like to discuss the principle of closed loop neuromodulation, implementation of the artificial regulators into the cardiovascular systems and renal denervation as well as baroreflex activation in managing refractory hypertension.

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